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MEETING ABSTRACTS

CHOLINESTERASES INHIBITED BY NOVICHOK AGENTS – *IN SILICO* STUDY OF REACTIVATION POSSIBILITIES

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Novichoks, subgroup of banned chemical warfare agents developed during Cold War in the Soviet Union are nerve agents (NAs) that irreversibly inhibit acetylcholinesterase (AChE) binding covalently to hydroxyl group of Ser-203 in the enzymatic active site (1). Currently, there are no known antidotes that are able to reactivate AChE inhibited by novichoks.

The aim of this study was to select potential reactivators able to restore vital AChE activity. Simultaneously, set of goals for potential reactivators was established:

(i) To determine whether a given ligand would be sterically suitable to interact with novichok A230 bound in the active site of AChE;
(ii) Select ligands with the highest affinity for the site and thus propose theoretical reactivation of complex AChE-A230.

Both molecular docking and molecular dynamics was used to visualise the active or blocked site of AChE, and to determine affinity values *in silico* modelling. Selection of 60 ligands (including commercially available reactivators, e.g. trimedoxime, asoxime) from peer-reviewed articles (2) were docked into into proximity of AChE-A230 complex bond using software AutoDock Vina (v. 1.1.2). The most promising 32 ligands docked in AChE were evaluated by molecular dynamics (GROMACS 2020.4 software).

Evaluation of specified simulations using Visual Molecular Dynamics (VMD) software has shown that the closest distance between the oxime group of the Z03-labeled ligand and the phosphorus of A230 was 3.14Å proposing theoretical successful reactivation regarding the near–attack conformation (NAC) criterion. The results of this study provide a rational basis for the synthesis of proposed reactivators and their consecutive *in vitro* evaluation.

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Keywords: novichok agents; acetylcholinesterase; reactivators; in silico

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